



Recommendations and Reports

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Pertussis Vaccination: Acellular Pertussis Vaccine for Reinforcing and Booster Use -- Supplementary ACIP Statement Recommendations of the Immunization Practices Advisory Committee

U.S. Department of Health and Human Services Public Health Service Centers for Disease Control
National Center for Prevention Services Division of Immunization Atlanta, Georgia 30333

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Centers for Disease Control William L. Roper, M.D., M.P.H., Director

The recommendations on pertussis were developed by the Immunization Practices Advisory Committee (ACIP), in collaboration with:

National Center for Prevention Services Alan R. Hinman, M.D., M.P.H., Director Division of Immunization Walter A. Orenstein, M.D., Director Vaccine Safety Activity Steven G. F. Wassilak, M.D., Chief

The production of this report as an MMWR serial publication was coordinated in:

Epidemiology Program Office Stephen B. Thacker, M.D., M.Sc., Director Richard A. Goodman, M.D., M.P.H., Editor MMWR Series

Scientific Communications Program Suzanne M. Hewitt, Chief Karen R. Bradfield, Writer-Editor Morie E. Miller, Editorial Assistant

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This supplementary statement provides information on and recommendations for the use of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). One such vaccine was recently licensed, ACEL-IMUNE. * This vaccine is licensed for use only as the fourth and fifth doses of diphtheria, tetanus, and pertussis vaccination; it is not licensed for the initial three-dose series in infants and children, regardless of age. At least one other DTaP product is anticipated to be licensed in the future for use as the fourth and fifth doses. The current Immunization Practices Advisory Committee (ACIP) statement on diphtheria, tetanus, and pertussis issued August 8, 1991, gives general recommendations on pertussis prevention, including the use of whole-cell pertussis vaccines for primary and booster vaccination (1).

INTRODUCTION

Current Whole-Cell Pertussis Vaccines

Simultaneous vaccination against diphtheria, tetanus, and pertussis during infancy and childhood has been a routine practice in the United States since the late 1940s. Whole-cell pertussis vaccines in the United States have been and continue to be prepared from suspensions of inactivated or disrupted *Bordetella pertussis* whole bacterial cells. Routine vaccination with whole-cell pertussis vaccines has been highly effective in reducing the burden of disease and deaths due to pertussis (3). Although the efficacy of each whole-cell vaccine in use in the United States has not been precisely estimated, clear evidence of overall high efficacy is available (4,5).

Whole-cell pertussis vaccines, although safe, are associated with a variety of adverse events, particularly local erythema, swelling and tenderness, fever, and other mild systemic events such as drowsiness, fretfulness, and anorexia (6,7). Infrequently, febrile convulsions and hypotonic-hypo-responsive episodes can occur after whole-cell DTP vaccination (6). The general concerns about safety have led investigators to attempt to develop safer pertussis vaccines that have high efficacy.

Acellular Pertussis Vaccines

General Information

Efforts have been under way for greater than or equal to 20 years to identify and purify the antigens of *B. pertussis* that can be incorporated into acellular pertussis vaccines that are protective, yet are less likely to induce reactions. In Japan, the initial impetus for the accelerated development of acellular pertussis vaccines was the occurrence in 1975 of two deaths in infants within 24 hours of DTP vaccination (8,9). These events led health authorities to temporarily suspend the routine use of whole-cell DTP vaccine in infants (then initiated at 3 months of age). Routine whole-cell DTP vaccination was rapidly reintroduced in most areas but recommended for administration at age greater than or equal to 2 years. However, vaccination coverage of children decreased, and the incidence of reported pertussis increased markedly, reaching a peak in 1979. Meanwhile, efforts to purify antigens of *B. pertussis* were accelerated. After limited clinical studies of immunogenicity and safety, several DTaP vaccines were licensed in Japan in 1981.

Since 1981, methods of purifying the antigenic components of *B. pertussis* have continued to improve, additional information on the protection of various antigens in animal models has accumulated, and candidate vaccines have been developed by many multinational manufacturers. Current candidate vaccines contain one or more of the bacterial components thought to provide protection. These components include filamentous hemagglutinin (FHA), pertussis toxin (PT -- also known as lymphocytosis promoting-factor, which is inactivated to a toxoid when included in a vaccine), a recently

identified 69-kilodalton outer-membrane protein (pertactin; Pn), and agglutinogens of at least two types (fimbriae (Fim) types 2 and 3). Several studies, relating to the immunogenicity and the safety of various candidate acellular pertussis vaccines, are currently being conducted or have been completed among children in the United States and other countries. In general, these vaccines, which are immunogenic, are less likely to cause common adverse reactions than the current whole-cell preparations (10-19).

The efficacy of two acellular pertussis vaccines developed by the Japanese National Institute of Health (JNIH) was studied during the period 1985 through 1987 in a randomized, placebo-controlled clinical trial in Sweden, a country in which pertussis vaccine had not been used routinely since 1979 (20). One vaccine (known in the trial as JNIH-6) contained 23.4 ug/dose each of pertussis toxoid and FHA. Another vaccine (JNIH-7), not similar to any vaccine used in Japan, contained only 37.7 ug/dose of pertussis toxoid. The 3,801 children who participated in this trial were randomly selected to receive two doses of an acellular pertussis vaccine (approximately 1,420 children in each vaccine group) or a placebo (954 children). Neither of the vaccines nor the placebo contained diphtheria and tetanus toxoids. The first dose of vaccine or placebo was administered to children 5-11 months of age; the second dose was administered 8-12 weeks later. Each vaccine demonstrated some degree of efficacy. For culture-confirmed disease with cough of any duration, the observed efficacy was 69% for JNIH-6 (95% confidence interval (CI), 47%-82%) and 54% for JNIH-7 (95% CI, 26%- 72%) (20). Levels of estimated efficacy were higher against culture-confirmed pertussis that was more severe and classic. The efficacy of JNIH-6 was 79% (95% CI, 57%-90%) and that of JNIH-7 was 80% (95% CI, 59%-91%) against culture-confirmed pertussis with cough lasting more than 30 days. However, direct comparisons with whole-cell pertussis vaccine were not available to determine whether one or both of these acellular vaccines conferred protection at least equivalent to that of whole-cell vaccine. This trial also demonstrated that the complexities of evaluating pertussis vaccine efficacy had changed substantially depending upon the case definition used (21-23). Specific serologic correlates of immunity were not identified in this study. It remains undetermined which vaccine components are most effective in inducing protection and which types of immune responses are most responsible for protection. During the trial, four participants died of invasive bacterial disease that occurred up to 5 months after vaccination. Three had received the JNIH-6 vaccine and one had received JNIH-7 vaccine; the significance of these findings is uncertain (24). Primarily because of concerns regarding the level of efficacy of the vaccine following vaccination, neither vaccine is licensed for use in Sweden (25).

Until now, acellular pertussis vaccines have been licensed for use only in Japan, where, since 1981, such vaccines have been administered routinely to children greater than or equal to 2 years of age (9). Studies of persons exposed to pertussis in household settings have demonstrated the effectiveness of several acellular pertussis vaccines manufactured in Japan in preventing clinical pertussis among children greater than or equal to 2 years of age (8,26-28). In Japan, with the continued use of acellular pertussis vaccines, the incidence of disease and death caused by pertussis has declined steadily. However, the reported incidence among children age less than 2 years has remained higher than the incidence among children of that age when whole-cell vaccines were routinely used in infants (9). Since 1989, vaccination of infants with Dtap beginning at 3 months of age has been initiated in many areas of Japan at the recommendation of the Ministry of Health. However, the extent of use among children less than 2 years of age remains low (S. Isomura, personal communication, 1991). Therefore, it is too soon to make conclusions about the effect of this policy on the age-specific incidence of pertussis among children less than 2 years of age.

Based on the experiences in Sweden and Japan, questions remain whether acellular pertussis vaccines confer clinical protection when administered early in infancy, or whether protection induced at any age is equivalent to that of whole-cell pertussis vaccine preparations. Consistent with the licensure of Dtap, the Committee recommends that whole-cell pertussis vaccine be continued for the initial three-dose vaccination series until an alternative vaccine is available that has demonstrated essentially equivalent or higher efficacy. To evaluate the relative protective efficacy of primary vaccination among infants, several clinical trials, which will compare Dtap vaccine with whole-cell DTP vaccine, are in progress or development.

ACEL-IMUNE Information

On December 17, 1991, the FDA licensed one Dtap vaccine for use as the fourth and fifth doses of the recommended DTP series. ACEL-IMUNE contains 40 mcg of protein; approximately 86% of this protein is FHA; 8%, PT; 4%, Pn; and 2%, Fim type 2. The acellular pertussis vaccine component is purified by ammonium sulfate fractionation and sucrose density gradient centrifugation; PT is detoxified by treatment with formaldehyde. Each dose of ACEL-IMUNE contains 7.5 limit of flocculation (Lf) of diphtheria toxoid, 5.0 Lf of tetanus toxoid, and 300 hemagglutinating (HA) units of acellular pertussis vaccine. The FHA and PT components both exhibit HA activity. The combined components are adsorbed to aluminum hydroxide and aluminum phosphate and preserved with 1:10,000 thimerosal.

Household exposure studies have demonstrated efficacy of acellular pertussis vaccines among children in Japan vaccinated at age greater than or equal to 2 years with the Takeda acellular pertussis vaccine component, combined with Takeda-produced diphtheria and tetanus toxoids (27-29). Clinical studies are in progress to examine the relative efficacy of ACEL-IMUNE in preventing disease when administered to infants at ages 2, 4, and 6 months compared with whole-cell DTP vaccine. The following evidence supports the use of ACEL-IMUNE after the initial infant three-dose series of whole-cell DTP vaccine.

Immunogenicity.

When ACEL-IMUNE is used for the fourth and fifth doses of the vaccination series, antibody responses after administration are generally similar to those following whole-cell DTP vaccine for the PT, Pn, and Fim components; antibody responses are higher for FHA ([Table 1](#)) (17,18).

Clinical efficacy.

In Japan, Takeda-manufactured Dtap vaccine has been shown to prevent pertussis disease among children age greater than or equal to 2 years, however, in this retrospective study clinicians and investigators were not blinded to the vaccination status of the participants (28). The occurrence of pertussis was compared in 62 children vaccinated with two to four doses of Takeda DTaP on or after the second birthday and 62 unvaccinated children for the period 7-30 days after household exposure to pertussis. Typical clinical pertussis occurred in one vaccinated child and 43 unvaccinated children; estimated clinical vaccine efficacy: 98% (95% CI, 84%-99%). Minor respiratory illness-possibly representing mild, atypical pertussis-occurred among an additional eight vaccinated and four unvaccinated children. When these children were included, the estimated vaccine efficacy was 81% (95% CI, 64%-90%). None of the vaccinated household contacts in this study were age less than 2 years; by restricting the analysis of results to household contacts who were age greater than or equal to 2 years, the corresponding estimates of efficacy were 97% (95% CI, 82%-99%) and 79% (95% CI, 60%-89%) respectively. In a smaller study of similar design, results were similar (29).

Safety.

Local reactions, fever, and other common systemic events occur less frequently after receipt of ACEL-IMUNE vaccinations than after whole-cell DTP vaccination. In general, local and common systemic events occur approximately one-fourth to two-thirds the frequency after whole-cell DTP vaccination ([Table 2](#)) (17,18). Available data indicate comparable safety for ACEL-IMUNE and Takeda DTaP packaged in Japan.

VACCINE USAGE

See the general ACIP statement on diphtheria, tetanus, and pertussis for more details (1). This vaccine is licensed only for use as the fourth and fifth doses of the DTP series among children ages 15 months through 6 years of age (before the seventh birthday). Use of DTaP is not recommended for children who have received less than three doses of whole-cell DTP, regardless of age. The Committee considers the first four DTP doses as primary immunization against diphtheria, tetanus, and pertussis. The fourth

(reinforcing) dose of DTP, generally given at age 15-18 months, is administered to maintain adequate pertussis immunity during the preschool years. The fifth (booster) dose of DTP is administered at ages 4-6 years of age to confer continued protection against exposure during the early years of school.

Either whole-cell DTP or DTaP can be used interchangeably for the fourth and fifth doses of the routine series of vaccination against diphtheria, tetanus, and pertussis among children greater than or equal to 15 months of age. The Committee recommends the use of DTaP, if readily available, because it substantially reduces local reactions, fever, and other common systemic events that often follow receipt of whole-cell DTP.

The standard, single-dose volume of ACEL-IMUNE is 0.5 mL and should be administered intramuscularly (IM).

Indications for the Fourth (Reinforcing) Dose

Six to 12 months after the third dose of DTP

One dose of DTaP (instead of whole-cell DTP) can be administered IM to children age 15-18 months (or later when necessary); this dose should be administered at least 6 months after the third dose of whole-cell DTP ([Table 3](#)). The fourth dose of either DTaP or DTP is an integral part of the primary immunizing course of pertussis vaccination. DTaP is not licensed for use among children age less than 15 months. Although immunogenicity data among children age 15-16 months are not yet available for ACEL-IMUNE, the Committee suggests that ACEL-IMUNE be used for children as part of the recommended schedule of routine simultaneous vaccination with DTP, oral poliovirus (OPV), and measles-mumps-rubella (MMR) at age 15-18 months (30).

Booster Vaccination

Children 4-6 years of age (up to the seventh birthday)

A dose of DTaP can be administered as the fifth dose in the series for children ages 4-6 years who either have received all four prior doses as whole-cell vaccine or for those children who have received three doses of whole-cell DTP and one dose of DTaP. A fifth dose of either DTaP or DTP should be administered before the child enters kindergarten or elementary school. The Committee recommends the use of DTaP, if readily available. This fifth dose is not necessary if the fourth dose in the series is given on or after the fourth birthday.

Special Considerations

Vaccination of infants and young children who have a personal or family history of seizures

Recent data suggest that infants and young children who have had previous seizures (whether febrile or nonfebrile) or who have immediate family members with such histories are at increased risk of seizures following DTP vaccination than those without such histories (1). Because these reactions may be due to the fever induced by whole-cell DTP vaccine and because DTaP is infrequently associated with moderate to high fever, use of DTaP is strongly recommended for the fourth and fifth doses if pertussis vaccination is considered for these children (see Precautions and Contraindications). A family history of seizures or other central nervous disorders does not justify withholding pertussis vaccination. Acetaminophen should be given at the time of DTP or DTaP vaccination and every 4 hours for 24 hours to reduce the possibility of postvaccination fever in these children.

Children with a contraindication to pertussis vaccination (see Precautions and Contraindications)

For children younger than age 7 years who have a contraindication to whole-cell pertussis vaccine, DT should be used instead of DTP; DTaP should not be substituted. If additional doses of pertussis vaccine

become contraindicated after a DTP series is begun in the first year of life, DT should be substituted for each remaining scheduled DTP dose.

Pertussis vaccination for persons age greater than or equal to 7 years

Adolescents and adults who have waning immunity are a major reservoir for transmission of pertussis (31). It is possible that booster doses of other preparations of acellular pertussis vaccines will be recommended in the future for persons age greater than or equal to 7 years, although it is not currently recommended.

SIDE EFFECTS AND ADVERSE REACTIONS

For a complete discussion, see the general ACIP statement on diphtheria, tetanus, and pertussis (1).

Although mild systemic reactions such as fever, drowsiness, fretfulness, and anorexia occur frequently after both whole-cell DTP vaccination and ACEL-IMUNE vaccination, they are less common after ACEL-IMUNE vaccination ([Table 2](#)). These reactions are self-limited and can be safely managed with symptomatic treatment.

Moderate-to-severe systemic events, including fever greater than or equal to 40.5 C (105 F); persistent, inconsolable crying lasting 3 hours or more; and collapse (hypotonic-hyporesponsive episode) have been rarely reported after vaccination with DTaP (16,20,32). Each of these events appears to occur less often than with whole-cell DTP. When these events occur after the administration of whole-cell DTP, they appear to be without sequelae; the limited experience with DTaP suggests a similar outcome.

In U.S. studies, more severe neurologic events, such as prolonged convulsions or encephalopathy, have not been reported in temporal association after administration of approximately 6,500 doses of ACEL-IMUNE. This somewhat limited experience does not allow conclusions to be drawn whether any rare serious adverse events will occur after administration of DTaP. Because DTaP causes fever less frequently than whole-cell DTP, it is anticipated that events such as febrile convulsions will be less common after receiving DTaP.

SIMULTANEOUS ADMINISTRATION OF VACCINES

The simultaneous administration of DTaP, OPV, and MMR has not been evaluated. However, on the basis of studies using whole-cell DTP, the Committee does not anticipate any differences in seroconversion rates and rates of side effects from those observed when the vaccines are administered separately. Although combinations have not been thoroughly studied, simultaneous vaccination with DTaP, MMR, OPV, or inactivated poliovirus vaccine (IPV), and Haemophilus b conjugate vaccine (HbCV) is acceptable; similarly, simultaneous vaccination with DTaP, hepatitis B vaccine (HBV), OPV, IPV, and HbCV is also acceptable. The Committee recommends the simultaneous administration of all vaccines appropriate to the age and the previous vaccination status of the child (30), including the special circumstance of simultaneous administration of DTP or DTaP, OPV, HbCV, and MMR at age greater than or equal to 15 months.

PRECAUTIONS AND CONTRAINDICATIONS

General Considerations

DTaP is licensed only for reinforcing and booster immunization -- the fourth and fifth doses in the DTP series. DTaP is not licensed for use among children age less than 15 months, on or after the seventh birthday, or for the initial three-dose series among infants and children regardless of their age.

Contraindications

Because no data currently exist to suggest otherwise, contraindications to further doses of DTaP are the same as those for the whole-cell DTP. If any of the following events occurs in temporal relation with the administration of DTP or DTaP, subsequent vaccination with DTP or DTaP is contraindicated:

1. An immediate anaphylactic reaction.
2. Encephalopathy (not due to another identifiable cause), defined as an acute, severe central nervous system disorder occurring within 7 days after vaccination and generally consisting of major alterations in consciousness, unresponsiveness, or generalized or focal seizures that persist more than a few hours, without recovery within 24 hours.

Precautions (Warnings)

If any of the following events occurs in temporal relation with the receipt of either whole-cell DTP or DTaP, the decision to administer subsequent doses of vaccine containing the pertussis component should be carefully considered. Although these events were once considered absolute contraindications to whole-cell DTP, there may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh the possible risks, particularly since the following events have not been proven to cause permanent sequelae:

1. Temperature of greater than or equal to 40.5 C (105 F) within 48 hours, not due to another identifiable cause.
2. Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours.
3. Persistent, inconsolable crying lasting greater than or equal to 3 hours, occurring within 48 hours.
4. Convulsions with or without fever, occurring within 3 days.

If these events occur after receipt of any of the first four

doses of whole-cell DTP vaccine and if additional doses of pertussis vaccine are indicated because the potential benefits outweigh the potential risks, consideration should be given to the use of DTaP for the fourth and fifth doses.

REPORTING OF ADVERSE EVENTS AFTER VACCINATION

As with any newly licensed vaccine, surveillance for information regarding the safety of DTaP in large-scale use is important. Surveillance information aids in the assessment of vaccine safety, although its usefulness is limited, by identifying potential events that may warrant further study. Additionally, specific evaluations of DTaP use in larger populations than those studied for license application are being initiated.

The Vaccine Adverse Event Reporting System (VAERS) of the Department of Health and Human Services became operational in November, 1990. VAERS is designed to accept reports of all serious adverse events that occur after receipt of DTaP, as well as any other vaccine, including but not limited to those mandated by the National Childhood Vaccine Injury Act of 1986 (33). Any questions about reporting requirements, completion of the report form, or requests for reporting forms can be directed to 1-800-822-7967.

- Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed is prepared and distributed as ACEL-IMUNE by Lederle Laboratories (Pearl River, New York) and was licensed December 17, 1991 (2). The acellular pertussis vaccine component is produced by Takeda Chemical Industries, Ltd. (Osaka, Japan), and is combined with diphtheria and tetanus toxoids manufactured by Lederle Laboratories.

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Table_1

Note: To print large tables and graphs users may have to change their printer settings to landscape and use a small font size.

Table 1. Comparison of immunologic responses to pertussis antigens among children vaccinated with ACEL-IMUNE(R) and among children vaccinated with whole-cell DTP given as the fourth DTP dose at 17-24 months of age and as the fifth DTP dose at 4-6 years of age *

Assay	% with >=4-fold increase 30 days after vaccination at 17-24 months of age		% with >=4-fold increase 30 days after vaccination at 4-6 years of age	
	ACEL-IMUNE(R)	Whole-Cell DTP	ACEL-IMUNE(R)	Whole-Cell DTP
Pertussis toxin + Filamentous hemagglutinin +	94 (N=36) &	74 (N=35)	84 (N=38)	88 (N=40)
Pertactin +	92 (N=36) &	60 (N=35)	97 (N=38)	85 (N=40)
Agglutination	81 (N=16)	89 (N=18)	86 (N=36)	68 (N=34)
	82 (N=34)	86 (N=35)	47 (N=32) &	72 (N=36)

* Among children previously vaccinated with whole-cell DTP, The number of specimens tested differ by assay. From Morgan CM, Blumberg DA, Cherry JD, et al., (17) and Blumberg DA, Mink CM, Cherry JD, et al., (18).

+ By enzyme immunoassay.

& P<0.05.

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Table_2

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Table 2. Comparison of frequency (%) of adverse events occurring within 72 hours after vaccination with ACEL-IMUNE(R) or whole-cell DTP among children given the fourth DTP dose at 17-24 months of age and the fifth DTP dose at 4-6 years of age *

Events	ACEL-IMUNE(R) N=911 +	Whole-Cell DTP N=178 +
Local		
Any erythema	29 &	50
Erythema>2 cm	10 &	21
Any induration	25 &	40
Induration>2 cm	7 &	12
Pain/tenderness	26 &	73
Systemic		
Fever >= 38 C (100.4 F)	19 &	26
Fever >= 39 C (102.2 F)	1.5	1.7
Antipyretic use	6 &	17
Drowsiness	6 &	22
Fretfulness	17 &	33
Vomiting	2 &	8

* Among children previously vaccinated with whole-cell DTP; from Morgan CM, Blumberg DA, Cherry JD, et al., (17) and Blumberg DA, Mink CM, Cherry JD, et al., (18) and manufacturer's unpublished data.

+ Of the 911 doses of ACEL-IMUNE(R), 778 were given as the fourth dose and 133 were given as the fifth dose; of the 178 doses of whole-cell DTP, the numbers were 89 and 89, respectively.

& P<0.05.

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Table_3

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Table 3. Routine diphtheria, tetanus, and pertussis vaccination schedule summary for children >7 years of age - United States, 1992

Dose	Age	Customary age/interval	Product
Primary 1	2 months	>= 6 weeks of age	DTP *
Primary 2	4 months	4-8 weeks after first dose +	DTP *
Primary 3	6 months	4-8 weeks after second dose +	DTP *
Primary 4	15 months	6-12 months after third dose +	DTaP or DTP *&
Booster	Age 4-6 years, before entering		DTaP or DTP *&

kindergarten or elementary school
(not necessary if fourth primary vaccinating
dose administered after fourth birthday)

Additional boosters Every 10 years after last dose Td @

* Use DT if pertussis vaccine is contraindicated. If the child is age ≥ 1 year at the time that primary dose three is due, a third dose 6-12 months after the second dose is administered completes primary vaccination with DT.
+ Prolonging the interval does not require restarting series.
& Either DTaP or whole-cell DTP can be used for the fourth and fifth doses; DTaP is generally preferred, if available.
@ Tetanus-diphtheria toxoids absorbed (Td) (for adult use).
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